Association Between Whole Blood Transfusion and Mortality Among Injured Pediatric Patients

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Objective: The aim of this study was to assess the association between whole blood (WB) and mortality among injured children who received immediate blood transfusion.

Background: The use of WB for transfusion therapy in trauma has been revisited, and recent studies have reported an association between WB and improved survival among adults. However, evidence of a similar association lacks in children.

Methods: We performed a retrospective cohort study from the American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) between 2020 and 2021. Patients were aged less than or equal to 16 years and had immediate blood transfusion within 4 hours of hospital arrival. Survival at 24 hours and 30 days were compared after creating 1:1 propensity score–matched cohorts, matching for demographics, injury type, vital signs on admission, trauma severity scores, hemorrhage control procedures, hospital characteristics, and the need for massive transfusion.

Results: A total of 2729 patients were eligible for analysis. The median age was 14 years (interquartile range: 8–16 years); 1862 (68.2%) patients were male; and 1207 (44.2%) patients were White. A total of 319 (11.7%) patients received WB. After a 1:1 ratio propensity score matching, 318 matched pairs were compared. WB transfusion was associated with improved survival at 24 hours, demonstrating a 42% lower risk of mortality (hazard ratio, 0.58; 95% CI, 0.34–0.98; $P = 0.042$) Similarly, the survival benefit associated with WB transfusion remained consistent at 30 days (hazard ratio, 0.65; 95% CI, 0.46–0.90; $P = 0.011$).

Conclusion: The use of WB was associated with improved survival among injured pediatric patients requiring immediate transfusion.

Keywords: child, hemorrhage, trauma, whole blood

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Trauma is a major cause of death among the young population.[1] Hemorrhagic shock is the largest contributor to death during the initial phase after a traumatic injury,[2] and it is second to traumatic brain injury (TBI) during the later period.[3] Among pediatric trauma patients, hemorrhagic shock and the need for blood transfusion have been identified as independent predictors for mortality.[4]

Over the past few decades, balanced resuscitation with conventional blood components has become the standard of care in adult trauma patients.[5] Similarly, a recent study reported that balanced blood component therapy was associated with improved mortality in the pediatric population.[6] Balanced blood component therapy provides a fixed ratio of blood components to replace blood loss with an approximation of reconstituted whole blood (WB). Among adult trauma patients, the recent adoption of WB for the initial resuscitation, compared with the standard balanced blood component therapy, has shown to be associated with improved patient survival.[7,8]

While the efficacy of WB in pediatric populations can be expected, because of limited sample sizes and the heterogeneity in injury patterns, scarce data are currently available.[9,10] Therefore, our study aimed to evaluate the efficacy of WB transfusion using large nationwide datasets. We hypothesized that the use of WB is associated with improved mortality.

METHODS

Study Design, Setting, and Data Source

This study was a retrospective cohort study which used coded data files from the American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) from January 2020 to December 2021. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, and a complete checklist has been provided in Supplemental Digital Content 1, Table 1 (http://links.lww.com/SLA/E937). The Institutional Review Board of the Japan Red Cross Maebashi Hospital approved the study as an exemption and waived the need for informed consent from patients, because the data were publicly accessible, retrospectively obtained, and deidentified.

Study Participants

We included injured pediatric patients (less than or equal to 16 years) who received blood transfusions within 4 hours after hospital arrival. Our exclusion criteria included (1) transfer from another hospital; (2) dead on hospital arrival; (3) Abbreviated Injury Scale of 6 in any body region; and (4) missing the mortality data.

Exposure and Primary Outcome Measure

We compared patients who received WB transfusion (WB group) with those who did not (no-WB group). Our primary outcome was in-hospital mortality at 24 hours and 30 days. Secondary outcomes selected a priori were hospital length of stay (LOS), intensive care unit LOS, and major complications. Major

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Authors' contribution: M.A. had full access to all study data and takes responsibility for the integrity of the data and accuracy of the data analysis. Concept and design; acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis: all authors. Drafting of the manuscript and supervision: M.A. and K.M. Administrative, technical, or material support: M.K. and K.M.

The authors report no conflicts of interest.

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complications included acute kidney injury, pulmonary embolism, deep vein thrombosis, acute respiratory distress syndrome, and stroke.

Covariates

Patient baseline characteristics included age, sex, race/ethnicity, injury type, payment type, age-adjusted shock, hypoxia, Glasgow Coma Scale, Abbreviated Injury Scale (head, chest, abdomen, and extremity), hemorrhage control procedures within 4 hours, teaching hospital status, number of hospital beds, and trauma center verification status (pediatric and/or adult). Age-adjusted shock was defined based on shock index, pediatric age adjusted.[11] Hemorrhage control procedures included laparotomy, thoracotomy, sternotomy, and extremity, neck, mangled extremity, other skin, or preperitoneal pelvic packing defined by TQIP-Data. Massive transfusion was defined as total blood transfusion volume per body weight >40 mL/kg during the first 4 hours of admission.[12]

Statistical Analysis

Continuous and categorical variables were reported as medians with interquartile ranges and counts with percentages, respectively. Patient-level and hospital-level characteristics were compared between the WB and no-WB groups using χ^2 and Mann-Whitney U tests for categorical and continuous data, respectively.

Propensity Score Matching

To account for potential confounders when assessing the association between WB use and in-hospital mortality, we created a propensity score for each patient and performed propensity score matching (PSM). The propensity score represented the predicted probability of receiving WB. It was determined using a logistic regression model for WB use as the dependent variable and the aforementioned covariates as the independent variables. Using a caliper of 0.2, the PSM extracted the 1:1 matched pairs of patients based on the propensity scores. Before and after PSM, the distributions of propensity scores between the WB and no-WB groups were examined. Match balance between the 2 groups was assessed using the absolute standardized mean difference.[13] We used the missing indicator method to handle the missing data. Missing values were coded as such, and a missing-value category was included as a separate category for the variable. In this way, the propensity score attempted to balance both the distribution of observed value and the distribution of missing data across the study groups.[14]

Statistical Analysis for Outcome Evaluation

First, we performed univariate analysis in the PSM patients between the WB and no-WB groups. Subsequently, a multivariable Cox proportional hazards regression model was created to evaluate the association between WB use and survival in both total and the PSM patients. Kaplan-Meier survival analysis for the primary outcome was performed and log-rank statistics were calculated. In addition, we performed several subgroup analyses to determine whether any observed association was dependent on a particular group of interest. These subgroups were developed based on age, mechanism of injury, age-adjusted shock, hemorrhage control, massive transfusion, and severe TBI. In each subgroup, multivariable Cox proportional hazards regression was performed, and interaction value was evaluated. Statistical significance was defined as a 2-sided P value <0.05 or assessed using a 95% CI. In the subgroup analysis, a significant interaction was defined as a P value <0.10.[15] Statistical analyses were performed using the R software (version 4.2.2; R Foundation for Statistical Computing).

RESULTS

A total of 2729 patients were identified during the study period (Fig. 1). Of those, 319 (11.7%) patients received WB in addition to other component blood products. Supplemental Digital Content 2, Table 2 (http://links.lww.com/SLA/E938). shows the patient-level and hospital-level characteristics in the WB and no-WB groups. In the total cohort, the WB patients were more likely to receive hemorrhage control procedures and massive transfusion. In the PSM cohort, all the absolute standardized mean differences were <0.1, and covariates estimating propensity scores were deemed well balanced.

The results of the univariate analysis are shown in Table 1. Both 24-hour and 30-day mortalities were significantly lower in the WB group (24-hour mortality, 7.3% vs 12.7%, $P=0.033$; and

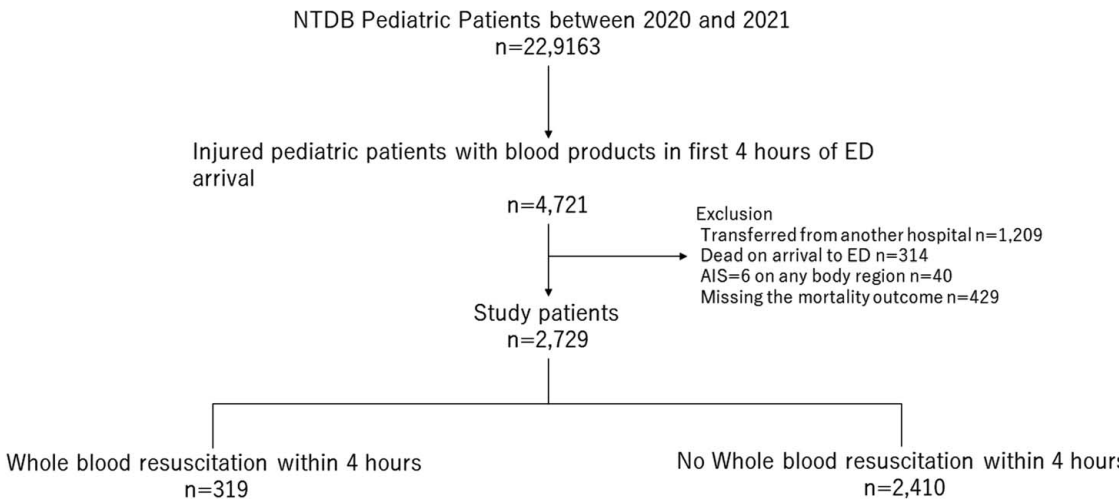
NTDB Pediatric Patients between 2020 and 2021
n=22,9163
Injured pediatric patients with blood products in first 4 hours of ED arrival
n=4,721
Exclusion
Transferred from another hospital n=1,209
Dead on arrival to ED n=314
AIS=6 on any body region n=40
Missing the mortality outcome n=429
Study patients
n=2,729
Whole blood resuscitation within 4 hours
n=319
No Whole blood resuscitation within 4 hours
n=2,410

FIGURE 1. Patient flow diagram. AIS indicates Abbreviated Injury Scale; ED, emergency department; NTDB, National Trauma Data Bank.

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TABLE 1. Study Outcomes Among PSM Patients

Outcome	WB group	No-WB group	*P*
Mortality			
24-h mortality [n (%)]	23 (7.3)	40 (12.7)	0.033
30-d mortality [n (%)]	62 (19.5)	86 (27.0)	0.031
ICU-LOS [median (IQR)]	4 (2–9)	5 (2–13)	0.100
LOS [median (IQR)]	9 (3–19)	10 (4–22)	0.132
Total transfusion [median (IQR)] (U)			
pRBC	1.13 (0–3.88)	3.00 (1.32–6.00)	< 0.001
Plasma	0 (0–2.96)	1.4 (0–4.00)	0.001
Platelets	0 (0–0.67)	0 (0–0.83)	0.066
Cryoprecipitate	0 (0–0)	0 (0–0)	0.480
WB	1.8 (1–2.1)	0 (0–0)	< 0.001
Total blood transfusion	4.2 (2.0–10.4)	4.47 (2.0–11.51)	0.292
Major complication [n (%)]			
AKI	7 (2.2)	6 (1.9)	1.000
Pulmonary embolism	5 (1.6)	2 (0.6)	0.451
DVT	16 (5.0)	7 (2.2)	0.087
ARDS	9 (2.8)	6 (1.9)	0.603
Stroke	5 (1.6)	4 (1.3)	1.000

AKI indicates acute kidney injury; ARDS, acute respiratory distress syndrome; DVT, deep vein thrombosis; ICU, intensive care unit; pRBC, packed red blood cell; TV, transfusion volume.

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30-day mortality, 19.5% vs 27.0%, $P = 0.031$). The volume of packed red blood cells and plasma transfusion was significantly lower in the WB group. No significant differences in hospital LOS and intensive care unit LOS were observed between the WB and no-WB groups. Similarly, the major complication rate was similar between the 2 groups.

The Kaplan-Meier survival analysis using log-rank test showed that WB transfusion was associated with increased probability of survival at 24 hours ($P = 0.027$) and 30 days ($P = 0.022$) (Figs. 2, 3). The results of multivariable Cox proportional hazards regression in the total and PSM patients are shown in Table 2. WB use was associated with reduced 24-hour mortality (hazard ratio, 0.58; 95% CI, 0.34–0.98) and 30-day mortality (hazard ratio, 0.65; 95% CI, 0.46–0.90) in the PSM cohort. In the subgroup analysis, all the interaction values were > 0.1 (Fig. 4). All estimate points were <1.0, and similar effects of WB were confirmed in all subgroups.

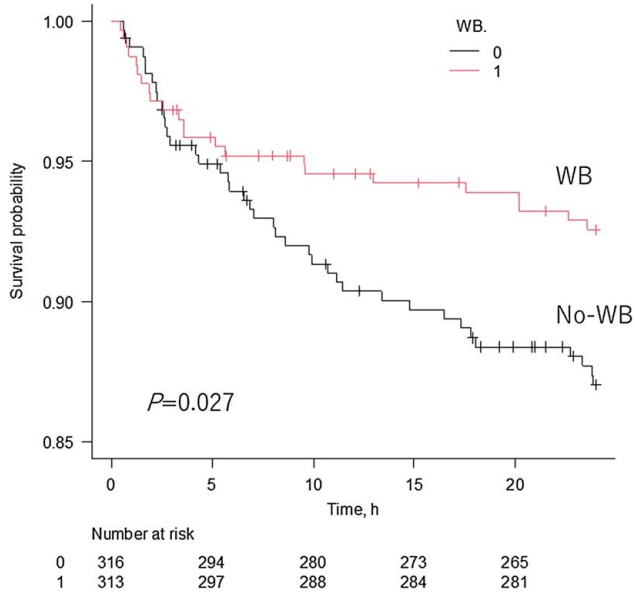

FIGURE 2. Adjusted Kaplan-Meier 30-day survival estimates.

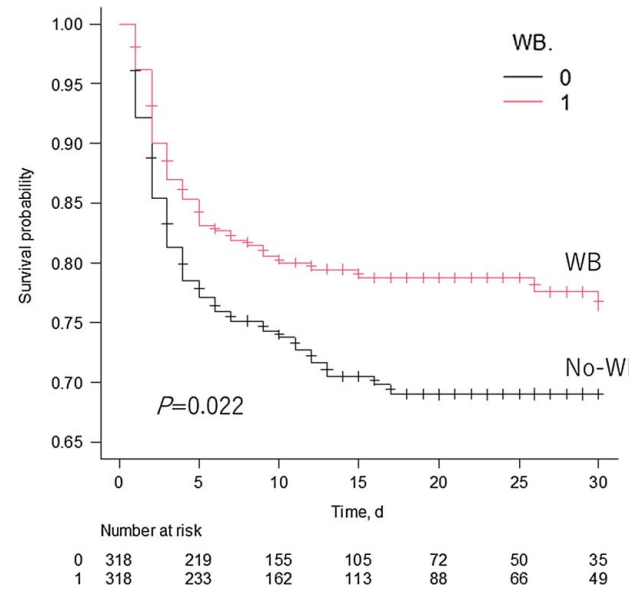

FIGURE 3. Adjusted Kaplan-Meier 24-hour survival estimates.

DISCUSSION

Using a nationwide dataset, this study showed that the use of WB was associated with improved 24-hour and 30-day mortality among pediatric patients requiring blood transfusion within 4 hours of arrival. Notably, the WB patients were more severely injured; however, the WB group was associated with a survival advantage after adjustment. Furthermore, we observed the survival benefit related to WB transfusion in different subgroups of the study patients.

WB transfusion in injured children has been shown to be associated with better outcomes, such as decreased blood transfusion requirements and ventilator days, faster resolution of shock, and lower posttransfusion international normalized ratio.[9,10] However, no survival benefit was shown in these previous studies.[9,10,16] The reason was thought to be its small sample size and the low mortality rate.[9] In a recent single-center study by Gaines et al,[17] WB transfusion was associated with improved survival in pediatric patients who received massive transfusion. To the best of our knowledge, our study was the first large cohort study to demonstrate the survival benefit of WB transfusion in pediatric trauma patients. In the current study, we found that only 36% (231/636) of the patients receiving WB transfusion ultimately required massive transfusion. Interestingly, the subgroup analysis showed that WB use was associated with improved survival even in patients who did not require massive transfusion. While the impact of WB transfusion on the total transfusion volume remains unknown in the pediatric population, the results of our study support the use of WB for all patients requiring early transfusion.

The current study showed that the point estimates of WB transfusion for 30-day survival were <1.0 in all subgroups, suggesting that the survival benefit related to WB transfusion could be expected in these subgroups of patients. While the

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TABLE 2. Adjusted Cox Proportional Hazards Regression

	Total patients (N = 2729)				PSM patients (N = 636)			
	Mortality at 24 h		Mortality at 30 d		Mortality at 24 h		Mortality at 30 d	
Treatment characteristics	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
WB	0.66 (0.43–1.01)	0.058	0.75 (0.58–0.98)	0.038	0.58 (0.34–0.98)	0.042	0.65 (0.46–0.90)	0.011
Age	1.01 (0.98–1.04)	0.383	1.00 (0.98–1.02)	0.417	1.02 (0.94–1.10)	0.575	1.01 (0.97–1.06)	0.477
Sex, male	1.08 (0.81–1.45)	0.582	0.98 (0.81–1.17)	0.836	0.79 (0.43–1.44)	0.445	0.77 (0.52–1.13)	0.188
Penetrating injury	2.32 (1.72–3.11)	< 0.001	1.95 (1.61–2.36)	< 0.001	2.49 (1.36–4.56)	0.003	2.22 (1.51–3.27)	< 0.001
Age-adjusted shock	0.89 (0.69–1.16)	0.040	0.89 (0.75–1.06)	0.206	0.71 (0.43–1.18)	0.188	0.75 (0.54–1.04)	0.088
Hypoxia	1.37 (1.03–1.83)	0.029	1.36 (1.13–1.64)	< 0.001	0.98 (0.54–1.78)	0.958	0.96 (0.65–1.42)	0.861
GCS < 9	9.39 (6.44–13.67)	< 0.001	12.81 (9.63–17.04)	< 0.001	14.99 (6.55–34.29)	< 0.001	17.76 (9.64–32.70)	< 0.001
Hemorrhage control	1.57 (1.20–2.06)	< 0.001	0.90 (0.74–1.08)	0.258	1.72 (1.03–2.88)	0.036	0.93 (0.66–1.30)	0.680
ISS	1.01 (0.99–1.67)	0.101	1.01 (1.00–1.02)	< 0.001	1.01 (0.99–1.03)	0.295	1.01 (1.00–1.03)	0.007
Trauma center								
ATC	1.26 (0.95–1.67)	0.101	1.18 (0.99–1.41)	0.062	1.73 (0.88–3.40)	0.114	1.48 (0.98–2.23)	0.059
PTC	0.88 (0.67–1.15)	0.362	0.87 (0.73–1.04)	0.130	1.00 (0.58–1.71)	0.992	1.14 (0.81–1.61)	0.444

ATC indicates adult trauma center; GCS, Glasgow Coma Scale; HR, hazard ratio; ISS, Injury Severity Score; PTC, pediatric trauma center.

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average age of our study cohort was higher than that of the study cohorts in previous studies,[10,17] we confirmed that the effect of WB transfusion was similar in a subgroup of patients with ages less than 12 years. In addition, survival benefit was confirmed in patients with severe TBI. More than one third of the PSM patients (235/636) had severe TBI, and our results may imply that transfusion can be effective in bleeding patients with severe TBI.

The combination of hemorrhagic shock and severe TBI is known to be associated with more severe coagulopathy[18]; therefore, any treatment to correct hemodynamic instability and coagulopathy should be not delayed. A report on the effect of WB transfusion in a combined TBI and hemorrhagic shock model, compared with blood component therapy, showed that the WB group had better neurological outcomes.[19] Early resuscitation with WB may be a preferred approach for this specific subgroup of patients.

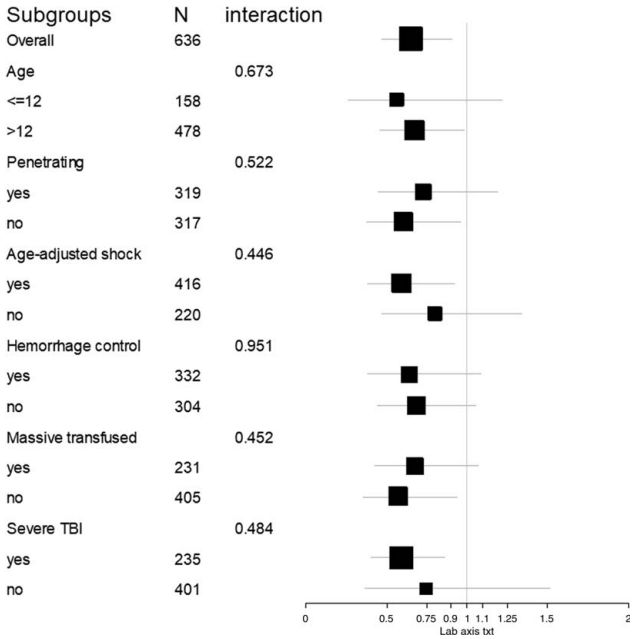

FIGURE 4. Adjusted hazard ratios in each subgroup.

Limitations

We acknowledge several limitations to this study. First, given the retrospective nature of the study, observed survival benefit associated with WB transfusion can only be interpreted as an association, not causation. While we conducted PSM to mitigate the risk of any potential bias, there remains a risk of unmeasured confounders affecting our results. Second, there may be significant institutional variations in the use of WB among TQIP centers. Hospital-specific identification codes are not included in the ACS-TQIP dataset, preventing us from accounting for clustering by facility. Instead, we adjusted hospital characteristics such as hospital type, number of beds, and trauma center level. Third, there is a potential risk of survival bias as the exact timing of WB administration was unknown. Patients who survived longer might have more frequently received WB transfusion. Finally, the patient demographics in this study suggest that a number of adolescent patients were included for our primary analysis. Although we performed the subgroup analysis in patients aged less than 12 years and found no interaction, the sample size was limited, thus further study is warranted to validate these results.

CONCLUSIONS

The use of WB for early transfusion therapy was associated with improved mortality in pediatric trauma patients. Future randomized controlled trials are warranted to validate the findings.

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